UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/486,313	06/07/95	WEISS S	

(H)

HM12/0121

IVOR R. ELRIFI
MINTZ,LEVIN, COHN,FERRIS, GLOVSKY AND
POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
CROUCH,T	

ART UNIT	PAPER NUMBER
1201	29

DATE MAILED: 01/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/486,313	Applicant(s) Weiss et al.
	Examiner Deborah Crouch	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Oct 28, 1998* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *26, 27, 32-37, and 39-59* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *26, 27, 32-37, and 39-59* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *24*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicant's arguments filed October 28, 1998 in paper no. 23 have been fully considered but they are not persuasive. The amendment has been entered.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26,32-35 and 40-58 provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-18,32,33,36,41-43 and 72 of copending Application No. 08/479,796. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 26,32-35 and 40-58 of the instant application overlap in subject matter with claims 16-18,32,33,36,41-43 and 72 of '796. Claims 26,32-35 and 40-58 are to methods of transplanting neural stem cell progeny into a host and claims 16-18,32,33,36,41-43 and 72 are to methods of providing cells to form myelin by administering multipotent neural stem cells. Both sets of claims contain limitations to culture with growth factors. As for the sites of implantation, the specific sites claimed in the instant application are within the scope of the implantation site claimed in '796. Thus the claims are obvious over each other, as the overlapping subject matter contains the limitations of both set of claims set forth above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 26,27,32-37 and 39-59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods of transplanting neural stem cell progeny into a host by obtaining a population of cells derived from mammalian neural tissue containing at least one multipotent CNS neural stem cell, where the neural stem cell produces progeny that differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or express galactocerebroside; culturing the neural stem cells in a culture medium containing one or more growth factors which indues multipotent neural stem cells proliferation; inducing proliferation of multipotent neural stem cells to produce neural stem cell progeny which includes multipotent neural stem cell progeny cells and transplanting said multipotent neural stem cell progeny into the host. The claims are not enabled as the transplantation of multipotent neural stem cell progeny into a host has not be demonstrated to provide any therapeutic benefit to the host. The specification clearly teaches that the use for the transplant method is for therapeutic effects to be provided to a host.

The specification at pages 36-42 discusses the use of multipotent neural stem cells in the treatment neurological disorders and CNS damage. The disclosure includes discussions of the use of xenogeneic cells or allogenic cells for the treatment of demyelination diseases or Parkinson's Disease as examples. The specification at pages 96-101 exemplifies the implantation of multipotent neural stem cell progeny into animal models of various neurodegenerative diseases. In some experiments the cells were transformed to contain DNA sequences encoding β-galactosidase. These animal models were for Parkinson's Disease, Huntington's Disease, stroke, cardiac arrest, spinal cord injury, epilepsy and Alzheimer's Disease. The multipotent neural stem cells administered were made as disclosed in the specification. The specification also discloses how and where the cells were administered.

However, in none of tables II-V does the specification provide for a therapeutic effect as a result of the implantation. While the cells did survive for some period of time, and those transformed produced β-galactosidase, this in not correlated with a therapeutic effect for any neurological disease or CNS damage. There is no guidance in the specification as to how many or how often the disclosed cells, transformed or not transformed, would need to be transplanted to obtain a therapeutic effect. While the specification provides the first steps to therapy, there is no guidance to provide for a reasonable expectation of success in transplantation of sufficient cells to obtain the disclosed therapy. Furthermore, given the teachings in the specification, the only use for the implantation is a therapeutic one. There is no other disclosed reason for the transplantation method provided. It is noted that example 15, page 68, shows the myelination of the spinal cord in myelin deficient rat. However, the degree of myelination by the implantation of multipotent neural stem cells is described as patchy (page 69, lines 22-25), and no effect on the rat is shown. The experiments were performed only on one day old myelin deficient rats. This would provide no guidance for older animals with an acquired neurodegenerative disease or CNS damage. Thus guidance is not present in the specification to teach how to use the method of transplantation without the skilled artisan engaging in an undue amount of experimentation and without a predictable degree of success. At the time of filing the art taught, that neuron replacement therapies were feasible for diseases such as Parkinson's and Huntington's disease (McKay, page 70, col. 2, lines 14-17). However, feasible does not mean enabled. Thus there at the time of filing there were no known therapies for the claimed methods of transplantation to be adaptable to. Further, the art also taught that the brain may need to be pretreated for efficient neuronal differentiation by engrafted stem cells (McKay, *ibid.*, lines 25-28). The specification does not provide any guidance on the pretreatment of the host brain to enhance the therapeutic outcome of the implanted multipotent neural stem cells.

Furthermore, the particular hormonal mix appears to be crucial in determining the type of cells neural stem cell progeny become. Cattaneo et al (1990) Nature 347, 762-765. Cattaneo et al teach a method of producing neural stem cells by dissecting rat embryo striatum primordia, and treating the cells with NGF and bFGF in serum-free media. The cell differentiate into neurons as indicated by the presence of nestin (page 762, col. 2, parag. 1, lines 7-18 and parag. 2, lines 9-12). Cattaneo et al also teach the incubation of bFGF alone (page 762, col. 2, parag. 2, lines 2-6). However, the conditions of Cattaneo do not teach the production of glia cells in the same culture. Thus the limitation in claims 26 and 52 to "suitable condition" is too broad given the teachings of Cattaneo et al of only neuronal development. The claims are not enabled for all suitable conditions. It also appears that the cells for proliferation were cultured only in serum free media (see ex. 3). Thus the claims, except for 36 is not enabled. The culture in serum free media may be important for maintaining the stem cell nature of the cells.

The amendments to the claims has overcome the previous rejections under 35 U.S.C. 112, second paragraph.

Claims 34 and 40 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 34 is broader in scope of "a fibroblast growth factor" than claim 32, which names only two of the members of fibroblast growth factor family.

Claim 40 is confusing because in claim 26, step (b), the differentiation results in the cells becoming both neurons and glia cells in the same culture, under the same conditions. The use of "and" means both. So, in claim 26 the neural cells are becoming both, and in

claim 40, the cells are becoming one or the other. The difference is important for the application of prior art. See below.

The amendment to the claims which states that the neural stem cells under suitable culture conditions produce progeny that differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or express galactocerebroside overcomes the rejection under 35 U.S.C. 103(a) made in the previous office action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 40 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Cattaneo et al (1990) Nature 347, 762-765. Cattaneo et al teaches a method of producing neural stem cells by dissecting rat embryo striatum primordia, which when treated with NGF and bFGF in serum-free media, developed into neurons as indicated by the presence of nestin (page 762, col. 2, parag. 1, lines 7-18 and parag. 2, lines 9-12). Cattaneo et al also teach the incubation of bFGF alone (page 762, col. 2, parag. 2, lines 2-6). The conditions disclosed by Cattaneo clearly teach the development of the neural stem cells into neurons. The expression of neuronal specific enolase or neurofilament would be and inherent property of the neurons produced by the method of Cattaneo et al. Thus Cattaneo et al. clearly anticipates claim 40 by teaching the production of neurons.

Claims 26,27,32-37,39, and 41-59 are free of the prior art. At the time of filing the prior art did not teach methods of transplanting neural stem cell progeny into a host, where

the progeny differentiate into neurons that express neuron specific enolase or neurofilament and glia that express glial fibrillary acidic protein or express galactocerebroside. The closest prior art is Cattaneo et al (1990) Nature 347, 762-765. Cattaneo et al teaches a method of producing neural stem cells by dissecting rat embryo striatum primordia, which when treated with NGF and bFGF in serum-free media, developed into neurons as indicated by the presence of nestin (page 762, col. 2, parag. 1, lines 7-18 and parag. 2, lines 9-12). Cattaneo et al also teach the incubation of bFGF alone (page 762, col. 2, parag. 2, lines 2-6). However, the conditions disclosed by Cattaneo only teach the development of the neural stem cells into neurons and not the development of the neural stem cells into neurons and glia cells as claimed. The wording of the claims means that the stem cells develop into both neurons and glia cells in the same culture, at the same time and under the same conditions.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Please note the change in art unit number to Art Unit 1632. Please use this art unit number on all correspondence.

Deborah Crouch

Dr. D. Crouch
January 16, 1999

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800 1630